SMOKELESS TOBACCO*

First Listed in the *Ninth Report on Carcinogens*

CARCINOGENICITY

The oral use of Smokeless Tobacco is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans which indicate a causal relationship between exposure to smokeless tobacco and human cancer (reviewed in IARC V.37, 1985; Gross et al., 1995).

Smokeless tobacco has been determined to cause cancers of the oral cavity. Cancers of the oral cavity have been associated with the use of chewing tobacco as well as snuff which are the two main forms of smokeless tobacco used in the United States. Tumors often arise at the site of placement of the tobacco.

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

In 1985, IARC determined there was inadequate evidence to indicate that smokeless tobacco is carcinogenic to experimental animals. Most reported studies had deficiencies in design. Subsequent studies have provided some evidence that snuff or extracts of snuff produce tumors of the oral cavity in rats. Smokeless tobacco products contain a variety of nitrosamines which have been shown to be carcinogenic to animals. The oral use of smokeless tobacco is estimated to be the greatest exogenous source of human exposure to these compounds. Nitrosamines are metabolically hydroxylated to form unstable compounds that bind to DNA. Extracts of smokeless tobacco have been shown to induce mutations in bacteria and mutations and chromosomal aberrations in mammalian cells. The oral cavity tissue cells of smokeless tobacco users have been shown to contain more chromosomal damage than those from nonusers (IARC V.37, 1985).

PROPERTIES

Chewing tobacco and snuff are the two main forms of smokeless tobacco used in the United States. Chewing tobacco consists of the tobacco leaf with the stem removed and various sweeteners and flavorings such as honey, licorice, and rum. Snuff consists of the entire tobacco leaf, dried and powdered or finely cut, menthol, peppermint oil, camphor, and/or aromatic additives such as attar of roses and oil of cloves (IARC V.37, 1985).

Chewing tobacco and snuff contain known carcinogens such as volatile and nonvolatile nitrosamines, tobacco-specific *N*-nitrosamines (TSNAs), polynuclear aromatic hydrocarbons, and polonium-210 (^{210}Po). These carcinogenic TSNAs are present in twice or more the concentration found in other consumer products (Brunnemann et al., 1986).

TSNAs, including 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and *N*-

* There is no separate CAS registry number assigned to smokeless tobacco.

nitrosonornicotine (NNN), present in tobacco and tobacco smoke are formed from nicotine and tobacco alkaloids. They are known carcinogens in laboratory animals. The concentrations of NNK and NNN, the most carcinogenic of the TSNAs, are high enough in tobacco and tobacco smoke that their total estimated doses to long-term snuff users and smokers are similar in magnitude to the total doses required to produce cancer in laboratory animals (Hecht and Hoffman, 1989).

Snuff stored at ambient room temperature (37 °C) for 4 weeks has shown a significant increase in TSNA levels. The TSNA levels rose from 6.24 to 18.7 ppm, nitrosamino acid (NAA) rose from 3.13 to 16.3 ppm, and volatile *N*-nitrosamines (VNA) rose from 0.02 to 0.2 ppm (Djordjevic et al., 1993).

USE

The use of smokeless tobacco probably dates back 7000 years and is found throughout the world. Snuff also had early beginnings. It was used in many of the European and Asian countries and in many cases the way it was carried, e.g. snuff boxes, was a sign of wealth and rank. North America accepted chewing tobacco in favor of snuff around the 1850s (IARC V.37, 1985).

After the USDA reclassified some chewing tobacco products as snuff in 1982, the male per-capita consumption of chewing tobacco in the United States was estimated to be 1.06 lb in 1983 (U.S. Department of Agriculture, 1984b; cited by IARC V.37, 1985).

Snuff is the only smokeless tobacco product that has had increasing sales in the United States (Djordjevic et al., 1993). In the three leading brands of snuff that account for 92% of the U.S. market, concentrations of nicotine and TSNAs were significantly higher than in the fourth and fifth most popular brands (Hoffman et al., 1995).

PRODUCTION

Chewing tobacco production in 1983 was reported to be 39,300 Mg or metric tons. This included plug, moist plug, twist/roll, and loose leaf. Snuff production increased between 1880 and 1930 from 4 million lb (1800 Mg) to more than 40 million lb (18,000 Mg) per year (Garner, 1951; cited by IARC V.37, 1985).

FTC (1997), in its sixth biennial report to Congress mandated by the Comprehensive Smokeless Tobacco Health Education Act of 1986, compiled U.S. sales figures for smokeless tobacco collected from the five largest manufacturers (99% of the market). Annual U.S. sales between 1985 and 1995 fluctuated between 114.4 million lb (51,900 Mg [metric tons]) in 1988 and 121.4 million lb (55,100 Mg) in 1985. The total 116.4 million lb (52,800 Mg) sold in 1995 comprised 54.6 million lb (24,800 Mg) loose leaf/chewing tobacco, 4.2 million lb (1900 Mg) plug/twist chewing tobacco, 4.5 million lb (2000 Mg) Scotch snuff/dry snuff, and 53.1 million lb (24,100 Mg) moist snuff. Moist snuff has shown the strongest increase in sales—nearly 50%—since 1986; it has been advertised the most heavily among the smokeless tobacco products.

REGULATIONS

Applicable regulations are given in detail in the Regulations table. Federal regulations

related to tobacco products that concern taxation, customs duties, and the potential for hand-to-mouth transfer of toxic substances when using tobacco in the workplace are not addressed in this section.

The U.S. Food and Drug Administration (FDA) regulates nicotine-containing cigarettes and smokeless tobacco products as nicotine-delivery medical devices under 21 CFR Part 897 "to reduce the number of children and adolescents who use these products and to reduce the life-threatening consequences associated with tobacco use." Measures to reduce the appeal of and access to cigarettes and smokeless tobacco products include numerous restrictions on advertising, including promotional items and event sponsorship. Tobacco-product-dispensing vending machines and self-service displays are prohibited except in adult establishments that do not allow children on the premises at any time. Retailers must request that persons up to the age of 27 present photographic identification bearing their birth date. Free distribution of tobacco products is prohibited. Each package and advertisement must bear the label "Nicotine-Delivery Device for Persons 18 or Older." Cigarettes may not be sold in packages of fewer than 20.

Analyses of FDA jurisdiction over tobacco products (cigarettes and smokeless tobacco products) have been published in the *Federal Register*, including 60 FR 41453-41787, August 11, 1995, with a correction at 60 FR 65349-65350; 61 FR 44615 ff., August 28, 1996; and 61 FR 45219-45222, August 28, 1996. FDA published Children and Tobacco Executive Summaries (U.S. FDA, 1996 a,b), which are available free on the Internet and by mail.

The Federal Trade Commission (FTC) of the Department of Commerce administers and enforces the Comprehensive Smokeless Tobacco Health Education Act of 1986, Public Law 99-252 (FTC, 1998). Regulations published in 16 CFR Part 307 include the requirement that one of three warning messages in regular rotation and distribution throughout the United States on packages of smokeless tobacco products and in their advertisements. One of the messages is "WARNING: THIS PRODUCT MAY CAUSE MOUTH CANCER." The requirements are given in detail in the Regulations table.

The Federal Communications Commission (FCC) shares responsibility with FTC for the ban of advertisements of cigarettes and smokeless tobacco on radio and television (FTC, 1998). A CFR citation was not located for 15 U.S.C. Sec. 4402(f), which banned, effective August 1986, advertising for smokeless tobacco products on any electronic communication medium subject to FCC jurisdiction.

The Centers for Disease Control and Prevention's (CDC) Office on Smoking and Health (OSH) is the delegated authority to implement major components of the DHHS's tobacco and health program, which comprises programs of information, education, and research. CDC's authority includes collection of tobacco ingredients information to facilitate HHS's overall goal of reducing death and disability from use of tobacco products (CDC, 1997). Manufacturers, packagers, and importers of smokeless tobacco products are required by the Comprehensive Smokeless Tobacco Health Education Act of 1986 (Public Law 99-252) to report to the Secretary of HHS the ingredients, including nicotine, in smokeless tobacco products. HHS is authorized to undertake research on the health effects of ingredients. CDC has published requests for comments in the *Federal Register* on its proposed data collection in 61 FR 49145-49147, September 18, 1996, and 62 CFR 24115-24116, May 2, 1997. CDC has also requested comments on an analytical protocol proposed for measuring the quantity of nicotine in smokeless tobacco products (62 FR 24116-24119, May 2, 1997, and 62 FR 29729, June 2, 1997). (These regulations were not final as of January 31, 1999.)

HHS, under 45 CFR Part 96—Subpart L—Substance Abuse Prevention and Treatment

Block Grant, requires that to be eligible for Block Grants to support substance abuse prevention and treatment services, each State must have in effect and strictly enforce a law that prohibits sale or distribution of tobacco products to persons under age 18 by manufacturers, distributors, or retailers.

Federal agencies have issued regulations to implement Public Law 104-52, the Prohibition of Cigarette Sales to Minors in Federal Buildings and Lands. Some agencies have not restricted their corresponding regulations to cigarettes. For example, the General Services Administration (41 CFR) and the Treasury Department (31 CFR) prohibit the vending and free distribution of tobacco products on property under their jurisdictions.

Under 32 CFR 85.6, health promotion efforts in each military service should include smoking prevention and cessation programs. Health care providers are encouraged to take the opportunity at routine medical and dental examinations to apprise service personnel of tobacco use risks (including smokeless tobacco) and how to get help to quit. Regulations are summarized in Volume II, Table A-34.